

## New Doors for the Endocrine Disease Management from the Molecular Perspective

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Pancreas produces digestive enzymes and hormones to control blood glucose balance in the body. This comprises of two segments. Exocrine tissue includes acinar cells and ductal system to carry the digestive juice till duodenum. Surrounded inside the exocrine tissues exist in extremely organized well-made elements called islets of Langerhans in which the five hormone secreting cells are assembled. A highly structured molecular program which is complex to regulate the allocation of cell progenitors towards mature endocrine cells during mouse pancreas genesis [1-4].

At the 13.5<sup>th</sup> embryonic day of gestation secondary transition occurs where pancreatic epithelium undergoes growth, branching and differentiation whereas on the 12.5<sup>th</sup> day of gestation fusion of ventral and dorsal pancreas take place. Multipotent progenitor cells marked by the expression of *Pdx1*, *Ptf1a*, *Cpa1*, and *c-myc* be present in tip of the branching epithelium which is seen through the Genetic lineage tracing experiments [5]. After the 14<sup>th</sup> gestational day the t progenitors separate as acinar, duct, and endocrine cell to finally limited to exocrine face [6,7].

It is still a controversial matter that if endocrine progenitors exist in the adult pancreas. The most important mechanism to regenerate insulin-producing cells, in injured and physiological situations, involves the ability of earlier  $\beta$  cells to self-replicate [8-10]. Intraislet progenitors and centroacinar cells are proposed as a site of islet neogenesis [11-14].

Studies of knockout mice deficient factors involved in pancreas growth made route for the formation of etiquettes to create insulin-producing cells from progenitor and embryonic stem cells [15].

Initial indication of growth of pancreas is seen as a dorsal and a ventral bulge at the connection of foregut or midgut. It is important to notice that *Isl-1* is essential in the mesenchyme, and in pancreatic epithelium to have the usual way of the growth and development of pancreas [16].

At the time of endocrine development *Notch2* was recognized as a vital factor behind the choice of endocrine cell destiny by *Ngn3* and pays to titrating RBP- $\kappa$  from *Ptf1a* [17]. Studies also show that *Notch* and *TGF- $\beta$*  signaling in similar pathways regulates pancreatic endocrine cell progenitor progress [18]. Unipotent and low replicating cells such as *Ngn3* expressing cells found through *in vivo* clonal analysis in mice might be having implications for the generation of insulin producing cells from progenitor cells or embryonic stem cells [19]. In the developing pancreas that separate into exocrine and endocrine cells, pancreatic epithelial cords would have the transcription factor *Sox9* [20].

Current trials where *Nkx6.1* forced expression was made in the endocrine pancreas discovered a notch-dependent and cross inhibitory mechanism working between *Nkx6.1* and *Ptf1a*, to give progenitor cells with ductal/endocrine or acinar cell fate, correspondingly [21]. The added control of multipotent pancreatic progenitor to ductal and endocrine destiny is manifested by the conjoint expression of *Sox9*

and HNF1 $\beta$  in embryonic cord cells [22,23]. Thus, the allocation to different cell fates is clearly made possible by the differential expression of transcription factors.

Compared to earlier presumed, *Ngn3* expression is seen persistent in adult islets, and genetic examination gives sign for the presence for this factor in the islet maturation and preserving activity of islet [24]. Loss of *Insm1* or *Rfx6* is go along with the resolution of mostly non distinguished islet progenitors is an important factor in endocrine cell subtype specification. Fascinatingly, alike *Ngn3*, the forced expression of *NeuroD1* in pancreatic progenitors in the control of the *Pdx1* promoter marks into differentiation to hormone producing cells, while the lack of the activity incites insulin producing beta-cells through apoptosis [25,26]. *Pax4* in glucagon producing cells can program alpha cells again as efficient beta cells which is able to counter chemically induced diabetes. It seems coupled function of *Pax4* and *Nkx2.2* is to lessen *Arx* gene action in primary committed beta-cells [27,28]. *Nkx2.2* was found involved in a repressor complex with *DNMT3*, *Grg3* and *HDAC1*, to promote beta-cell differentiation, and thus preventing destiny of alpha-cell [29].

The leading role of *MafA* in maturation of beta-cell is recognized by the control of its action by numerous pancreatic transcription features and together with *Nkx2.2*, *Nkx6.1*, *NeurD1*, *Foxa2*, *Pdx1*, *Pax6*, *MafB* and *Isl-1* [30].

Knowing details of regeneration of endocrine cells in the adult pancreas, the molecular mechanisms regulating endocrine pancreas development, functioning through islet neogenesis in pancreatic injury models might facilitate new possibilities to develop innovative methods for the treatment of diabetes mellitus. It is still not clear if stem/progenitor cells be present in pancreas of a human adult, also even if it is present, where is its location. The main process that makes the process of regeneration of insulin creating cells in a human pancreas is self-renewal of preceding beta-cells. Still, in several studies also intra islet progenitors were proposed to contribute to islet neogenesis. Numerous researches of pancreatic injury models, and transgenic mice, progenitor/stem cells were proposed to exist in in the duct epithelium, in which cells expressing the proendocrine marker *Ngn3* were identified. Regeneration capacity of alpha-cells, subsequent to changes in the glucagon signaling pathway is of interest for further studies [11].

Self-replication of preexisting beta-cells: Beta-cell production is related with aging, for example, regeneration capacity is therefore very much reduced in elder mice, when compared to young mice [31,32]. Beta-cell production in human being increases beta-cell mass, as seen from *in vitro* experiments where human islets were required to express the *Cdk4* gene [33,34]. Glucagon for Use as Potential Stem Cell of Endocrine Cell Regeneration: The Capacity of the adult endocrine pancreas to undergo regeneration is a controversial matter but there are evidences available.

Researchers have proposed increased prevalence of benign thyroid disease with low selenium status, but the optimal range of consumption is likely to be narrow, necessitating a careful method to recommending selenium supplementation. The effects of selenium supplementation might be facilitated through repletion of antioxidant or immune-modulating selenoproteins and polymorphisms in genes that encode selenoproteins might regulate vulnerability to supplementation. In chronic autoimmune thyroiditis, selenium supplementation decreases circulating levels of thyroid autoantibodies; yet, evaluation of clinically important primary outcomes has not revealed improvement and should be highlighted in future trials. Observational studies have shown that low selenium status is an iodine-independent risk factor for goitre; still, this finding has not been followed up by intervention trials in humans. In Graves' disease, selenium supplementation might enable biochemical restoration of euthyroidism and decrease ocular involvement, but these effects need to be established. Treatment with selenium supplementation is extensively used by clinicians across the spectrum of autoimmune thyroid diseases, in spite of the fact that it is recommended only in the treatment of mild Graves orbitopathy [35].

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